INTERMEDIATES FOR THE SYNTHESIS OF ANALOGUES OF ADRENAL CORTICAL HORMONES*

Trans-6-OXO-6,7,8,9-TETRAHYDRO-4,5-BENZINDANE AND 1,6-DIOXO-6,7,8,9-TETRAHYDRO-4,5-BENZINDANE

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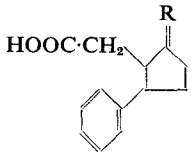
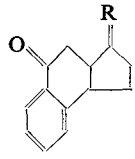
Previous assignments on mechanistic grounds of the stereochemistry of *trans*-6-oxo-6,7,8,9-tetrahydro-4,5-benzindane have been confirmed by degradation of a precursor to the known *trans*-2-carboxycyclopentane acetic acid. 1,6-dioxo-6,7,8,9-tetrahydro-4,5-benzindane has been shown to suffer autoöxidation in alkaline solution to yield 6-hydroxy-1-oxo-4,5-benzindane.

TOWARDS the synthesis of oxygenated 6,7,8,9-tetrahydro-4,5-benzindanes, the cyclisation of 2-phenylcyclopentane acetic acid (I,R = H_2) and its 5-oxo derivative (I,R = O) has been investigated. Starting material (I,R = O) was synthesised essentially by the method of Robinson[1], and on Wolff-Kishner reduction, furnished *trans*-2-phenylcyclopentane acetic acid (I,R = H_2). The stereochemistry of this was demonstrated by submitting (I,R = H_2) to destructive ozonolysis when the known *trans*-2-carboxycyclopentane acetic acid[3] resulted. Previous assignments[2,4,5] of *trans* stereochemistry to (I,R = H_2) are thus directly confirmed.

Cyclisation of (I,R = H_2) was smoothly accomplished with anhydrous hydrogen fluoride to give *trans*-6-oxo-6,7,8,9-tetrahydro-4,5-benzindane (II, R = H_2)[4,5]. Likewise under the same conditions, 5-oxo-2-phenylcyclopentane acetic acid (I,R = O) yielded 1,6-dioxo-6,7,8,9-tetrahydro-4,5-benzindane (II,R = O). The acid (I,R = O) was shown to be stable under the alkaline conditions used in the Wolff-Kishner reduction and is also assigned a *trans* configuration; for obvious reasons, however, this does not necessarily apply to the tricyclic product (II, R = O) resulting on ring closure. The constitution of the cyclised products (II,R = H_2 and O) was confirmed by reduction of the carbonyl groups followed by dehydrogenation. 4,5-benzidane[6] was obtained in both cases.



(I)



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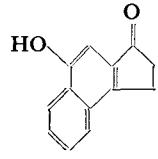
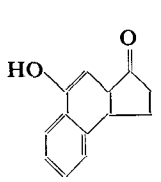


(III)

* Cf. Cowell and Mathieson, *J. Pharm. Pharmacol.*, 1957, **9**, 549; Coles, Linnell, Mathieson and Shoukri, *J. chem. Soc.*, 1954, 2617.



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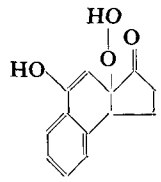

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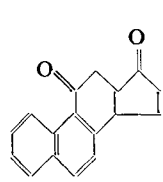

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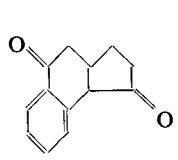

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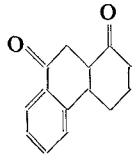
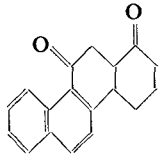
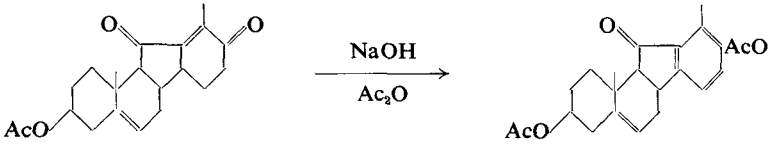


(VIII)



(IX)

Since under the usual conditions—sodamide in liquid ammonia—neither α-tetralone nor 6-oxo-6,7,8,9-tetrahydro-4,5-benzindane (II,R=H_2) would react with sodium acetylide, it was hoped in the case of (II,R = O) to react only the ketone at C (1) with this reagent. Analogues of 11-oxo steroids would then have been available. Instead, the compound suffered dehydrogenation and an almost quantitative yield of 1-oxo-6-hydroxy-4,5-benzindane (III) resulted. This almost complete conversion of (II,R = O) to (III) precludes disproportionation of any intermediate form such as the monoenolic dihydronaphthalene (IV). Involvement of oxygen moreover was indicated by the fact that (II,R = O) was stable in alkaline solution provided all oxygen was excluded from the system. When shaken with oxygen in 0·5N sodium hydroxide, two atoms of gas were absorbed for each mole of the compound and the resulting solution gave tests indicative of peroxides. Since neither *trans*-6-oxo-6,7,8,9-tetrahydro-4,5-benzindane (II,R = H_2) nor the isomeric 1-oxo compound underwent oxidation in this wise, the course of aromatisation may be one of hydroperoxide formation involving attack at C(8) (cf. V); activation both by the enol from C(6) and by the C(1) ketone being necessary. Breakdown of the hydroperoxide would then follow to yield in this case the substituted naphthalene (III). Oxidation of the identically constituted naphthindane (VI)[7] provides a similar example of this type of reaction and undernoted transformation of an aetiojervine derivative[8] may likewise be of a similar type.



The susceptibility of such a system to oxidation of this kind was demonstrated with the compounds shown above, (VII), (VIII) and (IX), all of which readily absorbed oxygen in alkaline solution. Uptake of gas, however, did not cease at two atoms per mole and as much as 10–15 moles were recorded. No definite products could be isolated from the resulting

solutions and oxidation of the third ring is probably involved in the case of (VIII) and (IX). Examination of the ultra-violet absorption spectra of the crude products in these two cases indicated an extension of conjugation from the simple benzene chromophore originally present.

1,9-Dioxo-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (VIII) was synthesised by cyclisation of the previously described[11] 6-oxo-2-phenylcyclohexylacetic acid. Our constants of the diketone (VIII) are in agreement with those found by Nasipuri[12] who recently synthesised this compound independantly by an identical route.

Experimental

Trans-2-*phenylcyclopentane acetic acid* (I,R = H_2). 1-Oxo-3-phenylcyclopentane-2-acetic acid[2] (20 g.) in diethylene glycol (200 ml.) was refluxed for 45 minutes under nitrogen with potassium hydroxide (16 g.) and 50 per cent w/v hydrazine hydrate (22 ml.). Sufficient water was then distilled off to raise the temperature of the solution to 195° and this temperature was maintained for 2 hours. On working up in the usual manner there resulted (17 g. of a dark viscous liquid which was purified by slowly passing an ethereal solution through a charcoal column. The resulting colourless gum crystallised from light petroleum (b.p. $< 40°$ at $-30°$ to give colourless needles m.p. 40–40·5° (lit.[4] cites b.p. 115–125°/0·02 mm.). (Found: C, 76·5; H, 7·9·calc. for $C_{13}H_{16}O_2$, C, 76·9; H, 7·9 per cent.)

The *anilide* of the above acid crystallised from benzene/light petroleum (b.p. 60–80°) in colourless needles m.p. 82–84°. (Found: C, 81·6; H, 7·5; N, 5·0. $C_{19}H_{21}ON$ requires C, 81·2; H, 7·4; N, 4·9 per cent.)

The *amide* crystallised from benzene/light petroleum (b.p. 60–80°) in colourless needles m.p. 80–80·5°. (Found: C, 76·9; H, 8·3; N, 6·9. $C_{13}H_{17}ON$ requires C, 76·7; H, 8·4; N, 6·9 per cent.)

Ozonolysis. Ozone was bubbled through the above acid (1 g.) in glacial acetic acid (20 ml.) for 5 hours; 3 per cent hydrogen peroxide solution (50 ml.) was evaporated almost to dryness on the water bath, a further 25 ml. hydrogen peroxide solution was then added and the process repeated. The residue was then added and the mixture left overnight. The solution was dissolved in aqueous sodium carbonate (20 ml.) and neutral material extracted with ether. Acidification of the alkaline layer and ether extraction yielded *trans*-2-carboxycyclopentane acetic acid crystallising from light petroleum (b.p. $< 40°$) m.p. 62–64° (lit.[3] cites m.p. 66°).

Trans-6-oxo-6,7,8,9,-tetrahydro-4,5-benzindane (II, R = H_2). 2-Phenylcyclopentane acetic acid (700 mg.) was dissolved in anhydrous hydrogen fluoride (30 ml.). After 10 days, evaporation of the reagent gave a neutral residue crystallising from ethanol in needles m.p. 88–89° (yield 90 per cent) (lit.[5] cites m.p. 79–82°).

λmax in ethanol 248 mμ (ϵmax 13,400), 293 mμ (ϵmax 2,000), νmax in carbon tetrachloride 1,695 cm.$^{-1}$.

The oxime crystallised from ethanol in colourless needles m.p. 183–189 (lit.[5] cites m.p. 181°). The 2,4-dinitrophenylhydrazone crystallised from

xylene in dark red plates m.p. 246–247°. λmax (main band in chloroform) 387 mμ (εmax 28,100) (lit.[5] cites m.p. 242–244°).

1,6-*Dioxo*-6,7,8,9-*tetrahydro*-4,5-*benzindane* (II, R = O). 1-Oxo-3-phenylcyclopentane-2-acetic acid (4·2 g.) was treated with hydrogen fluoride as described above: a neutral residue was obtained which crystallised from light petroleum (b.p. 80–100°) in colourless needles (2·35 g.) m.p. 107–109° after sublimation at 120°/0·2 mm. (Found: C, 78·0; H, 6·0. $C_{13}H_{13}O_2$ requires C, 78·0; H, 6·0 per cent.) λmax in ethanol 248 mμ (εmax 12,100), 293 mμ (εmax 1800). νmax in carbon tetrachloride 1,760 cm.$^{-1}$. (C = O in 5 membered ring) 1,705 cm.$^{-1}$ (aryl ketone). The *dioxime* crystallised from aqueous ethanol in long needles m.p. 171–173°. (Found: C, 67·8; H, 6·1; N, 12·1. $C_{13}H_{14}O_2N_2$ requires C, 67·8; H, 6·1; N, 12·2 per cent.)

4,5-*Benzindane*. The above dioxobenzindane (1·6 g.) in toluene (60 ml.) was reduced with zinc amalgam (20 g.) in water 25 ml. and concentrated hydrochloric acid (35 ml.). From the organic layer there was recovered a mobile colourless oil, 6,7,8,9-tetrahydro 4,5-benzindane[9] (0·85 g.) b.p. 72°/0·05 mm. This was refluxed for 4 hours with 30 per cent palladium on charcoal. Extraction with ether yielded a mobile oil with a blue fluorescence. The ultra-violet spectrum of this was identical with that of an authentic sample of 4,5-benzindane. A picrate was obtained in orange-red needles, m.p. 107–108°: this gave no depression on admixture with an authentic sample.

Autoöxidation experiments. (i) 1,6-Dioxo-6,7,8,9-tetrahydro-4,5-benzidane (II, R = O) (1·04 g.) in ethanol (250 ml.) was added to a 5 per cent aqueous solution of potassium hydroxide (250 ml.) and allowed to stand for 4 hours. Acidification of the light yellow solution gave a crystalline residue (1·02 g.) m.p. 280–284°. A sample of this (390 mg.) was chromatographed on a column of alumina grade I (76 g.). After placing on the column with benzene, 44 mg. of a gum was eluted (20 per cent in benzene) followed by a single peak (340 mg.) m.p. 289–291°: this gave no depression on admixture with an authentic specimen of 6-hydroxy-1-oxo-4,5-benzindane (III) prepared by ring closure of 1-oxo-3-phenylcyclopentene-2-acetic acid. The acetate crystallised in colourless prisms m.p. and mixed m.p. with an authentic sample[10] 163–164°. The ultra-violet absorption spectra of the two samples of (III) were identical: λmax in ethanol 223, 262, 290, 362 mμ (εmax 27,600, 37,500, 4,500, 5,800).

(ii) The above diketone (30 mg.) in 0·5N sodium hydroxide in ethanol (10 ml.) was shaken with oxygen in a microhydrogenation apparatus of conventional design. Oxygen (3·07 c.c. at N.T.P.) was steadily absorbed in 14 minutes when uptake ceased. This corresponds to 2 atoms oxygen per mole of diketone used. When uptake of gas had ceased the solution gave a blue colour with acidified starch iodide paper and gave a positive perchromic acid test.

(iii) When the above experiment was repeated with nitrogen in place of oxygen, starting material 1,6-dioxo-6,7,8,9-tetrahydro-4,5-benzindane was recovered quantitatively.

(iv) When ethanol alone was used as a solvent no uptake of oxygen occurred and starting material was again recovered unchanged.

1-*Oxo*-3-*phenylcyclohexane*-2-*acetic acid.* 6-Oxo-2-phenylcyclohexene-1- acetic acid (II) (4 g.) in ethanol (60 ml.) was hydrogenated at 5 per cent palladium on strontium carbonate (800 mg.). The residue (3·9 g.) obtained on evaporation of the solvent was crystallised from benzene/light petroleum (b.p. 40–60°) then from aqueous acetic acid in fine colourless needles m.p. 140–141° (lit.[11] cites m.p. 136–137°). Low melting fractions were converted to the above form by warming to 50° for 3 hours under nitrogen with N sodium hydroxide. (Found: C, 72·9; H, 6·9. Calc. for $C_{14}H_{16}O_3$, C, 72·4; H, 6·9 per cent.)

The semicarbazone crystallised from ethanol in fine colourless needles m.p. 206–207° (lit.[11] cites m.p. 192–193°).

The 2,4-*dinitrophenylhydrazone* crystallised from aqueous acetic acid in yellow needles m.p. 242° (darkens at 235°). (Found: C, 58·5; H, 4·9; N, 13·7. $C_{20}H_{20}O_6N_4$ requires C, 58·3; H, 4·9; N, 13·6 per cent.

1,9-*Dioxo*-1,2,3,4,9,10,11,12-*octahydrophenanthrene.* The above acid (1 g.) was allowed to stand for 5 days in anhydrous hydrogen fluoride (30 ml.). Evaporation yielded a residue which sublimed at 100–105°/0·2 mm. Crystallised from aqueous methanol this gave colourless needles m.p. 150–151°. Found: C, 79·3; H, 6·7. $C_{14}H_{14}O_2$ requires C, 78·5; H, 6·6 per cent.) νmax 1,730 cm.$^{-1}$, 1,708 cm.$^{-1}$ in carbon tetrachloride: λmax 249 mμ (ϵ11,000) in ethanol. The *bis* 2,4-*dinitrophenylhydrazone* crystallised from nitrobenzene in crimson needles m.p. 290° (decomp.). (Found: N, 19·8. $C_{26}H_{22}O_8N_8$ requires N, 19·5 per cent.)

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